REMARKS

The rejection of claims 7-9, 19, 20, 27, 29, 31, 33, and 37-42 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Adair *et al.*, Kipriyanov *et al.*, Pack *et al.*, and Hodits *et al.* was maintained in the January 24, 2006 Advisory Action. In the PTOL-303 form of the Advisory Action, a checked box indicates that for Purposes of Appeal the proposed amendments will not be entered. For purposes of clarification, contrary to the indication in the Advisory Action, there were no proposed amendments in Applicants first Response After Final.

This Response is submitted with a Request for Continued Examination and the required fee. Also filed concurrently herewith under separate cover is an Information Disclosure Statement which contains a copy of the Kipriyanov *et al.* publication discussed hereinbelow.

In this Response and Request for Continued Examination, Applicant has amended claim 7 and has added new claim 43. Support for the amendment to claim 7 is present throughout the originally filed specification and drawings, including for example on page 13, lines 1-2 of the published application WO99/27964 ("The cloned scFv sequence can be humanized to make it less immunogenic or nonimmunogenic to a human host."). Support for new claim 43 is present throughout the originally filed specification and drawings, including for example on page on page 4, lines 22-25 of the published application WO99/27964.

The amendment to claim 7 and addition of claim 43 has not been made in response to any rejection or any assertion by the Patent Office relating to patentability, but merely for the purpose of covering commercial embodiments. Accordingly, *Festo* has no applicability and the Doctrine of Equivalents is fully applicable to all aspects of claim 7 and the additional new claim 43. Claims 7-10, 19, 20, 27, 29, 31, 33, and 37-43 are therefore pending. Applicant requests entry of this Amendment and consideration of the Remarks made herein.

Rejection Under 35 USC § 103

Claims 7-9, 19, 20, 27, 29, 31, 33, and 37-42 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Adair *et al.*, Kipriyanov *et al.*, Pack *et al.*, and Hodits *et al.* Applicant reiterates the traverse as set forth in the October 11, 2005 Response After Final. Applicant also submits the following Remarks in support of the traverse.

Pending claim 10 was not indicated as being rejected in the description of the rejections in the January 24, 2006 Advisory Action, the Final Rejection dated April 11, 2005, or the first Office Action mailed May 21, 2004. However, claim 10 is listed with the rejected claims in PTOL-303 form of the Advisory Action. Applicant requests clarification of this inconsistency. The Examiner acknowledges that Adair *et al.* does not teach a multivalent recombinant antibody having more than two antigen binding sites (May 21, 2004 Office Action, page 3). However, in the January 24, 2006 Advisory Action the Examiner asserted that Kipriyanov *et al.* "teaches that increasing the valancey of a molecule increases the binding affinity of the molecule (see Table 2, page 209)". As noted above, Applicant traverses this rejection and requests reconsideration in view of the Remarks presented below.

The increase in binding valency of the multivalent molecules said to be described in Kipriyanov *et al.* is not relevant to the claimed invention

The Examiner has not provided evidence that Kipriyanov *et al.* or Pack *et al.* on their face contain any motivation or suggestion to modify a monoclonal antibody like the one reported in Adair *et al.* to make it multivalent. Instead, in making the rejections under 35 USC §103, the Examiner appears to be relying on his or her own interpretation of the cited references formed subsequent to examining Applicant's claimed invention.

The claims in the instant application are directed to a multivalent recombinant antibody against ICAM-1 "wherein said antibody is polymerized through a coiled-coil sequence"(claim 1). Kipriyanov *et al.* reports "a procedure for reconstituting active antigen-binding tetrameric antibodies formed by fusing a single-chain Fv to self-association core strepavidin." The single-chain Fv subunits are polymerized by this core strepavidin, which is totally different than being polymerized by a coiled-coil sequence. The Examiner appears to take the position that the increased affinity allegedly achieved in the scFv::strep molecules reported in Kipriyanov *et al.* are applicable to any multivalent molecule, including those which were not made or tested in Kipriyanov *et al.* This position is incorrect because the geometry, size, and other physical and chemical properties of the strepavidin linker and scFv molecules reported in Kipriyanov *et al.* have no bearing or relevance in making other multivalent binding molecules. As first discussed in Applicant's November 22, 2004 Response, the affinity at which a multivalent antibody is capable of binding a ligand is a function of the geometry of the antibody as it relates to a

particular ligand. Indeed, authors of both Kipriyanov *et al.* and Pack *et al.* recognized this and reported the same in publications they coauthored. In a publication coauthored by Kipriyanov, it was reported that the avidity of bivalent, trivalent, and tetravalent binding proteins is a function of the length of the peptide molecule that joins each scFv binding partner (Le Gall *et al.* FEBS Letters 453 (1999), 164-168, not cited by the Examiner. Copy included with Applicant's IDS dated May 11, 2006). This article reports that "the observed tetramerization might be dependent on the particular antibody fragment and its folding history." [1] This publication reports the binding affinity of dimers, trimers, and tetramers, and states "Surprisingly, triabodies demonstrated the worst antigen binding characteristics among the examined scFv fragments." This data, including the showing that a trimer has a lower affinity than a dimer, disputes the notion relied upon by the Examiner that binding affinity is a direct and predicable function of the valency of a binding molecule without regard to what linker is used to make the antibody multivalent. Similarly, Pack *et al.*, discussed in greater detail below, reports that the gain in stability of antibody-antigen complexes is strongly influenced by geometric factors. Applicant respectfully submits that the increased binding affinity reported in Kipriyanov *et al.* cannot be applied to the teaching of Adair *et al.* to achieve the instant claimed multivalent recombinant antibody which is polymerized through a coiled-coil sequence.

---

[1] See page 167 of Le Gall *et al.* FEBS Letters 453 (1999) 164-168, which reports

"As expected, scFv-10 formed mainly dimers and scFv-0 formed only trimers (Fig. 3b, d). Both were shown to bind CD19 by flow cytometry. In contrast to previously described sc Fv fragments containing the V_H domain linked to V_L via Ser^{113} that formed either dimers [7] or trimers [11,20], our scFv-1 exclusively formed tetrameric molecules with apparent molecular mass of 115 kDa (Fig. 3c). The tetramerization of such scFv antibody fragments with one residue linker is described here for the first time. Since our HD37 effectively forms dimers even with a linker of 18 residues (Fig. 3a), the observed tetramerization might be dependent on the particular antibody fragment and its folding history [21].

Multiple binding to surface-bound antigens is dependent on both the correct orientation of V_H-V_L pairs in a multivalent antibody complex and on epitope accessibility. Surprisingly, triabodies demonstrated the worst antigen binding characteristics among the examined scFv fragments. These results suggest that the anti-CD19 triabody can only bind monovalently to its cell surface anchored antigen. Inhibition experiments demonstrated and increase in affinity for scFv-10 (diabody) and scFv-1 (tetrabody) (Fig. 4b, Table 1), but only the tetrabody had a significantly lower dissociated rate compared to a monovalent binder (bispecific diabody) from the cell surface active antigen binding sites, only two of them seem to be involved in binding cell anchored CD19."

The Kipriyanov *et al.* publication also fails to provide an enabling disclosure, which is required for a reference to qualify as prior art. For example, Kipriyanov *et al.* fails to teach the making of multivalent antibody molecules which are folded correctly, which have the desired biological activity, and which can be obtained in an amount and purity sufficient for therapeutic administration. Kipriyanov *et al.* acknowledges significant problems in obtaining multivalent antibody molecules which were folded correctly. Kipriyanov *et al.* reports "The majority of our expressed fusion protein formed insoluble aggregates in E. Coli cells that could only be dissolved under strong denaturing conditions (6M GuHCL). Even under these conditions, some of the scFv::strep molecules were still present as oligomers formed by the by the strepavidin moiety." Thus, it appears that only a small portion of the scFv::strep molecules which were correctly folded were multivalent. Kipriyanov *et al.* fails to report whether it obtained enough biologically active protein to be useful for therapeutic purposes. Kipriyanov *et al.* also fails to suggest that scFv::strep proteins can be used for therapeutic purposes. The low yield of tetramers, combined with the fact that the affinity of the antibodies described in Kipriyanov *et al.* was significantly less than that specified in the claimed embodiments, would lead one of skill in the art to expect that applying the teachings of Kipriyanov *et al.* to Adair *et al.* would fail to produce an antibody having utility for therapeutic purposes.

Kipriyanov *et al.* is not properly combinable with Adair *et al.*

One of skill in the art would not combine what Kipriyanov *et al.* fairly teach or suggest with Adair *et al.* for the reasons discussed below. The strepavidin linker used in Kipriyanov *et al.* would be incompatible with producing an antibody that i) has utility for a therapeutic use (claims 19, 20, 27, 29, 31, 33) , or which is ii) made and/or altered to be less immunogenic or nonimmunogenic in humans (claims 7-10, and 37-42). This is because a scFv::strep fusion protein, or any other multivalent antibody that used strepavidin as a linker, would be highly immunogenic in a human and thus unsuitable for therapeutic uses. Specifically, it would be expected to elicit an immune response in humans that would destroy the fusion protein and render it dysfunctional, in particular where administered in repeat doses. (see page 7 of Applicant's November 11, 2005 Response After Final).

This inherent immunogenicity of a fusion protein that incorporates strepavidin, as taught by Kipriyanov *et al.*, is inconsistent with purpose and teachings of Adair *et al.* As the title of Adair *et al.* suggest, "Humanized CDR-Grafted Anti-ICAM-1 Antibodies, Methods of Preparation and Usage Thereof", the problem addressed was to make an antibody which, by being humanized, had a minimal Human Anti-Mouse Antibody (HAMA) response when used as a anti-rhinoviral therapeutic in humans.[2] Applying the teachings of Kipriyanov *et al.* would defeat this goal because it would render the antibody much more immunogenic.

Accordingly, one of skill in the art would not be motivated to apply the teachings of Kipriyanov *et al.* in an attempt to modify an antibody of Adair *et al.* to make it multivalent. Furthermore, one of skill in the art would expect that following the teachings of Kipriyanov *et al.* would destroy the desired properties of claimed embodiments of Applicant's invention.

One of skill in the art would further be discouraged from combining the teachings of Adair *et al.* and Kipriyanov *et al.* because the molecule reported in Adair *et al.* is a recombinant monoclonal antibody (derived from a murine monoclonal (R65-D6) having specificity for ICAM-1. See page 23, lines 13-15, page 31, lines 23-25, pages 45-54 of the Material Methods section of published WO91/16927, and claim 11), while Kipriyanov *et al.* relates only to scFvs. Kipriyanov *et al.* reports "A major disadvantage of scFv, however, is the monovalency of the product, which precludes an increased avidity due to polyvalent binding." (page 203, first sentence of second paragraph of Introduction). However, this low binding affinity is not an art recognized problem generally associated with monoclonal antibodies. As such, the problems addressed in Kipriyanov *et al.* are inapplicable to the Adair *et al.* disclosure and one of skill in the art would not be motivated to combine the teachings of Kipriyanov *et al.* with those of Adair *et al.*

Pack *et al.* is not properly combinable with Adair *et al.*

[2] See page 19, lines 3-11 of WO91/16927, which reports "Currently available anti-ICAM-1 MAbs, which are the basis of the above described methods of treatment, are murine MAbs and as a result are likely to cause a significant HAMA response if administered in repeat doses to human patients. It would be highly desirable to diminish or abolish this undesirable HAMA response by suitable humanization or other appropriate recombinant DNA manipulation of these potentially highly useful antibodies and thus extend and enlarge their use. It would also be desirable to apply the techniques of recombinant DNA technology to these antibodies to prepare anti-ICAM-1 RAMs in general."(emphasis added)

One of skill in the art would not combine Pack *et al.* with Adair *et al.* for the reasons discussed below. Pack *et al.* further corroborates Applicant's position discussed above that the structure, geometry, valency, and affinity of each multivalent antibody and epitope must be independently evaluated in designing and making any particular multivalent binding molecule. Pack *et al.* reports "The gain in stability of antibody-antigen complexes depends on the thermodynamic affinity of a single binding site (intrinsic affinity), the number of binding sites per molecule and the number of epitopes within reach, and its strongly influenced by geometric factors (Crothers & Metzger, 1971; Kaufman & Jain, 1992)." (emphasis added). Neither Kipriyanov *et al.* nor Pack *et al.* provide any teaching regarding geometric factors that would be applicable to the humanized murine monoclonal antibody to ICAM-1 reported in Adair *et al.*

Like Kipriyanov *et al.*, the tetravalent miniantibodies reported in Pack *et al.* are based upon single–chain Fv fragments. While a scFv and a monoclonal antibody can be said to be generally related, they are quite different structurally. An scFv is a single chained polypeptide which is much smaller than an intact monoclonal antibody and contains only portions of a monoclonal antibody, such as the one described in Adair *et al.* This accounts for the low binding affinity of an scFv. As is the case with Kipriyanov *et al.*, the problems purported to be addressed in Pack *et al.* are not applicable to the Adair *et al.* disclosure. Only with hindsight to Applicant's invention would one look to Kipriyanov *et al.* and/or Pack *et al.* to modify the Adair *et al.* disclosure to make a multivalent recombinant antibody against ICAM-1 based upon an scFv molecule.

Kipriyanov *et al.* and Pack *et al.* both fail to make any report or suggestion to use streptavidin (as in Kipriyanov *et al.*) or a flexible linker (as in Pack *et al.*) to join together two monoclonal antibodies to comprise three or more antigen binding sites, or four as is the case of a tetravalent molecule. Neither reference teaches or fairly suggest that the approaches they describe are applicable to monoclonal antibodies, as opposed to a scFv. Furthermore, a linker agent suitable for causing four scFvs to form a tetravalent molecule would not be expected by one of skill in the art to be useful in linking two monoclonal antibodies according to Adair *et al.* together to function as a tetramer. One of skill in the art would not expect such a molecule to achieve a geometry that would allow the two linked monoclonal antibodies to bind a particular ligand with a greatly enhanced affinity. Undue experimentation would be required by those of

skill in the art to attempt to apply the teachings of Kipriyanov *et al.* and Pack *et al.* to modify the humanized antibody of Adair *et al.* to achieve a an antibody having a 10-fold higher affinity than the antibody described in Adair *et al.*

Hodits *et al.* is not properly combinable with Adair *et al.* and fails to teach the claim elements required to support a rejection

Hodits *et al.* purports to be directed to an antibody fragment against the low density lipoprotein receptor (LDL) that inhibits rhinovirus infection (Abstract). Hodits *et al.* reports bivalent scFv7 molecules that are made bivalent by binding two molecules "via the myc-sequence tag which is COOH terminally fused to the antibody fragment."(page 24084). The alleged bivalent molecules of Hodits *et al.* are totally different than those of the instant invention. In order to become bivalent, they require a separate antibody that recognized tag sequences. The attachment of the scFv7 molecules, mediated by antibodies, would result in a totally different geometry as compared to a molecule utilizing a coiled-coil polymerization domain according to the claimed embodiments of the instant invention. Accordingly, one of skill in the art would not be motivated to combine Hodits *et al.* with Adair *et al.* in an attempt to achieve the instant invention. Moreover, the Examiner has not provided any showing that Hodits *et al.* teaches an antibody having an apparent affinity constant for the LDL receptor of no less than 10^8 M^{-1}, let alone in a formula which also contains an anti-ICAM-1 antibody having an apparent affinity constant for ICAM-1 of no less than 10^9 M^{-1} (claims 29 and 33).

The references in combination do not suggest or make obvious the claimed invention

Even if one were to combine the teachings of Adair *et al.*, Kipriyanov *et al.*, Pack *et al.*, *and* Hodits *et al.*, such a combination would neither suggest nor make obvious Applicant's claimed invention. "To establish a *prima facie* case, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference or

references, when combined, must teach or suggest all the claim limitations. MPEP 706.02(j), citing, In re Vaeck, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991) (emphasis added).

To establish a *prima facie* case of obviousness based on a combination of the content of various alleged references, there must be some objective teaching, suggestion or motivation in the prior art to make the specific combination. *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). The teachings of the alleged references, their relatedness to the field of the applicant's endeavor, and the knowledge of persons of ordinary skill in the field of the invention, are all relevant considerations. *See In re Oetiker*, 977 F.2d at 1447, 24 USPQ2d at 1445-46; *In re Gorman*, 933 F.2d at 986-87, 18 USPQ2d at 1888; *In re Young*, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). .

Moreover, obviousness can not be established by hindsight combination to produce the claimed invention. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As discussed in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the alleged prior art itself, and not the applicant's achievement, that must establish the obviousness of the combination. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."). It has been held that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine any alleged prior art references.

Additionally, in order for a document to qualify as prior art the reference must be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention. *See, e.g., PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter" (emphases added)).

Applying the law to the current facts, the Examiner has failed to complete a *prima facie* case as required under 35 U.S.C. §103. One of skill in the art would not look to Kipriyanov *et*

al. or Pack *et al.* for guidance in methods to modify Adair *et al.* to make it multivalent so that it comprised three or more antigen binding domains for ICAM-1. One of skill in the art would not be motivated to combine the teachings of Kipriyanov *et al.* or Pack *et al.* with those of Adair *et al.* One of skill in the art would also not have an expectation of success of producing the claimed invention based upon the insufficiency of the teachings of Kipriyanov *et al.* and Pack *et al.*

Assuming for the sake of argument that one attempted to modify Adair *et al.* and combine its teachings with that of Kipriyanov *et al.*, Pack *et al., and* Hodits *et al.*, it is doubtful that such a molecule would have any biological activity. There has been no showing that combining two humanized monoclonal antibodies of Adair *et al.* with the flexible hinge of Pack *et al.* would result in a multivalent antibody having a geometry that would allow it to bind ICAM-1 with an affinity constant of no less than 10^9 M^{-1}. Similarly, the affinities reported in Kipriyanov *et al.* would have no bearing on the affinity of the multivalent antibody that used the flexible hinge of Pack *et al.* If a streptavidin linker reported in Kipriyanov *et al.* were used, there is no indication that the resulting multivalent antibody would have a geometry allowing the molecule to achieve the claimed affinity for ICAM-1, and such a recombinant antibody would be more immunogenic in humans as opposed to less.

For these reasons, Applicant respectfully submits that the limited teachings of Kipriyanov *et al.*, Pack *et al., and* Hodits *et al.* fail to supply the deficiencies of what Adair *et al.* teach or suggest. Applicant respectfully observes that it appears that the Examiner has used improper hindsight to view these references and reconstruct Applicant's invention in support of the instant rejection under 35 U.S.C. §103. Accordingly, Applicant requests that the rejection under 35 U.S.C. §103 be reconsidered and withdrawn.

CONCLUSION

For the reasons set forth above, Applicant respectfully submits that all pending claims in the application are in condition for allowance. The Examiner is encouraged to contact the undersigned if it is believed this would expedite prosecution. For the reasons described and supported above, Applicants respectfully submit that all pending claims are now in condition for allowance. That said, should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at (619) 744-2240 so that they may be promptly resolved.

In the unlikely event the transmittal letter is separated from this document and the Office determines that an extension and/or other relief is required, Applicants petition for any required relief, including extensions of time, and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to the credit card disclosed in form PTO-2038 filed with this document

Respectfully submitted,

By: _____
James W. Collett, Ph.D.
Reg. No. 46,636

DUANE MORRIS LLP
101 West Broadway, Suite 900
San Diego, CA 92101-8285
(O) 619.578.2200
(F) 619.744.2201

694119v1.doc